Original Article

Predictive power of Koplik's spots for the diagnosis of measles

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Abstract

Introduction: Measles is a major cause of mortality globally. In many countries, management of measles is based on clinical suspicion, but the predictive value of clinical diagnosis depends on knowledge and population prevalence of measles. In the pre-vaccine era with high measles incidence, Koplik's spots (KS) were said to be "pathognomonic". This study prospectively evaluated test properties and diagnostic odds ratios (OR) of KS.

Methodology: Data including KS status were prospectively collected for a six-month period on all suspected measles cases reported to the North-West London Health Protection Unit. Saliva test kits were sent to all cases and KS test properties were analysed against measles confirmation by PCR or IgM testing (gold standard).

Results: The positive predictive value (PPV) of clinically suspecting measles was 50%. Using KS as diagnostic tool improved the PPV to 80% and the presence of KS was associated with confirmed measles in the multi-variable analysis (OR 7.2, 95% Confidence Interval 2.1-24.9, p=0.001).

Conclusion: We found that Koplik's spots were highly predictive of confirmed measles and could be a good clinical tool to enable prompt measles management and control measures, as action often needs to be taken in the absence of laboratory confirmation. We suggest that current clinical case definitions might benefit from the inclusion of KS.

Key words: (MeSH); measles; Koplik's spots; epidemiology; predictive value

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Introduction

Measles remains a major cause of morbidity, particularly in developing countries [1] and is a leading global cause of child death. The World Health Organisation (WHO) has therefore issued a global plan for the reduction of measles, focusing on vaccination strategies [2]. In spite of the improving measles vaccination coverage globally, decreasing coverage has been observed in some countries due to economic hardship, political instability, natural disasters and safety concerns about vaccines[3], leading to sharp increases of measles cases in countries such as Ivory Coast, Philippines, Iraq and also in the United Kingdom [1,4].

Clinical and public health actions have to be appropriate and timely. Highly sensitive laboratory tests are available in some countries [5,6], but usually diagnosis relies on clinical presentation. Moreover, laboratory results may take several days for diagnosis confirmation and vary according to the availability of test kits, transport and laboratory lead times. Decisions on clinical and public health interventions, such as isolation, vitamin A treatment, vaccination of contacts and the administration of immunoglobulins to pregnant contacts, are therefore regularly made in the absence of laboratory results.

Available clinical case definitions, such as those from WHO (any person with fever and maculopapular rash and cough, coryza or conjunctivitis), are often devised for surveillance purposes [7] and therefore have high sensitivity. However, these case definitions may generate false positives and therefore have a low predictive value for confirmed measles [8], especially in low prevalence areas. The American paediatrician Henry Koplik described red spots with a blue-white speck in the buccal mucosa (Koplik's spots) as a "pathognomonic" sign for measles in the pre-vaccine era and published his findings in case-series studies [9]. Koplik's spots (KS) have recently been described in measles [10], but they were also noted in other viral illnesses such as Parvovirus B19 or Echovirus

[11,12]. There are no published studies systematically examining the sensitivity, specificity, positive and negative predictive value (NPV) of this clinical test and they are not included in the WHO clinical case definitions [7].

The aim of this study was twofold: first to formally evaluate the test properties of Koplik's spots (KS) in a situation of rapid increase in disease incidence following relatively low prevalence rates, and secondly to assess whether the inclusion of KS in clinical case definitions may improve its test properties and therefore guide timely and appropriate clinical and public health response before laboratory confirmation becomes available.

Methodology

We prospectively collected clinical and laboratory data on all measles cases reported to the North-West London Health Protection Unit (NWLHPU) during six successive months in 2008. Notification on suspicion is a statutory requirement in the UK, even if measles is considered alongside other differential diagnoses. Staff were trained to proactively obtain information on KS from the reporting clinician and before laboratory confirmation. The recent measles epidemic in London led to increased confidence to recognise clinical signs of measles including KS.

Data were entered onto the routine database, held on a secure server within the health protection unit and anonymized for analysis. All suspected measles cases received a postal saliva swab kit with instructions for self-swabbing, using the Oracol Saliva System (Malvern Medical Developments Ltd, Worcester, UK) for oral fluid samples [6]. This is routine follow-up as part of national policy in England.

Samples were returned to the Health Protection Agency (HPA), for laboratory testing via a provided return envelope. We considered detection of measles-specific IgM (ELISA) or measles RNA (PCR) in oral fluid or serum as laboratory confirmation of measles [5].

Statistical analysis was performed with the statistical software package STATA 9.2. A complete case analysis was performed, and missing data was excluded before entering analysis. Proportions were compared by Chi-Square tests, continuous variables with Student T-tests if the assumption of normal distribution was justified, using logarithmic transformation if appropriate for right skewed distributions, and the Wilcoxon rank sum test for non-transformable distributions (*e.g.*, delays between symptoms or rash to reporting). We calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and 95% confidence intervals (CI) for KS as a diagnostic tool for measles. We also analysed diagnostic odds ratios in a forward built logistic regression model to analyse the strength of association between possible predictors and confirmed measles diagnosis [13].

Results

During the observation period, 190 suspected measles cases were reported to the NWLHPU. About 49% of the notifications were received from General Practitioners (UK family doctors, GPs) and 42% from hospital doctors; the remainder came from other health professionals. Diagnosis confirmation by saliva swab was sought for all patients and swab results were available for 131 (69%) of them.

Information on KS was available for 90 suspected cases and laboratory results were available for 68 (76%) of these. This is slightly below national average (85% in 2008-2009) [14] and similar to London testing proportions. There were no major differences between cases where information on KS was available compared with those where this information was missing by age ($p = 0.4$), sex ($p = 0.9$), or source of report (general practice versus hospital, $p = 0.14$). Equally, suspected cases with laboratory results were similar in age ($p = 0.3$) and sex ($p = 0.3$) compared to those without.

The median time between rash onset and reporting was one day (interquartile range, IQR 1-3). There was no difference in reporting delay by setting (between hospital doctors and GPs, $p = 0.9$). Only one single case can be considered fully vaccinated and had previously received the recommended two doses of an effective measles vaccine.

The overall PPV of clinically suspecting measles ($n = 131$) was 50% (CI 42-59%), lower for GPs (19%, CI 6-31%) than for hospital doctors (63%, CI 49-78%). Using KS as a diagnosis tool improved the PPV for confirmed diagnosis to 80% (CI 71-89%). The PPV for diagnosing measles using KS remained higher for hospital doctors (86%, 95% CI 75-97%) compared with GPs (50%, CI 32-68%, Table 1).

Using logistic regression, we found that KS and setting were highly predictive variables for correct diagnosis (Table 2). Although the mean age of patients seen in hospital was higher compared with general practice ($p = 0.0001$), age was not a predictor of correct diagnosis (log-likelihood ratio test, LR-

Table 1. Summary of test properties and 95% confidence intervals (brackets) for Koplik's spots in the diagnosis of confirmed measles

	All reports	Hospital doctors	General practitioners
Sensitivity	62.5% (51-74%)	69.2% (54.9-83.5%)	33.3% (16.2-50.5%)
Specificity	86.1% (78.4-94.6%)	78.6% (65.9-91.3%	91.3% (81.1-100%)
PPV	80.0% (70.6-89.4%)	85.7% (74.9-96.6%)	50.0% (31.8-68.2%)
NPV	72.7% (62.2-83.2%)	57.9% (42.6-73.2%)	84.0% (70.7-97.3%)

N = 68 (complete case analysis)

Test p = 0.1), but this could be due to a lack of statistical power for age-specific analysis. Likewise, differences in rash-to-reporting times (LR-Test p = 0.6) or sex (LR-Test p = 0.4) were not associated with measles diagnosis and not included in the final model. The number of vaccinated individuals with confirmed measles (n = 1) was too small to allow inclusion in the model. We did not find evidence of interaction between any of these variables, and allowing for age mix or reporting delays did not explain the higher predictive values of KS in hospital compared to general practice settings.

Discussion

To our knowledge this is the first study that attempts a systematic evaluation of the test properties of KS. Our study demonstrates that Koplik's spots were highly predictive of confirmed measles and could be a timely tool to enable prompt management and control measures prior to laboratory confirmation. Current case definitions used by the World Health Organization (WHO) are designed for surveillance purposes [7]. These definitions are highly sensitive to ensure notification of all possible cases, but do not necessarily provide optimum guidance for clinical and public health management.

For clinicians and public health practitioners, it is equally important to consider false positives, for example, in cases of scarlet fever, which would require antibiotic treatment. False positives may arise as a consequence of the low specificity and positive predictive value of the WHO case definitions, particularly in settings where knowledge of measles is limited, for example, due to relatively low baseline incidence [15]. Therefore, using these case definitions may be of limited value for the clinician and public health practitioner who may not have laboratory tests available to guide initiation of appropriate treatment or prophylaxis [16,17].

Public health interventions such as school exclusion and vaccinations of contacts are often taken if measles cases are confirmed or deemed probable. Possible cases, where the indications for a diagnosis are not very strong, are usually followed up with close observation rather than immediate public health action, with the exception of opportunistic interventions, such as the recommendation of vaccination for wide social networks aiming for a general increase in population immunity. Our results suggest that suspected measles cases presenting with Koplik's spots should be treated as probable cases and lead to the immediate introduction of the full range of clinical and public health interventions that would be taken for confirmed measles cases.

KS had a substantially lower predictive value for diagnosing measles in general practice compared to hospitals. This is likely to be driven by the overall lower predictive value of measles cases in primary care compared to hospitals, but independent of other factors, such as age, sex or reporting delays. Possible explanations include the lower setting-specific prevalence of measles cases among all rash-illnesses in primary care, or clinical experience.

There have been occasional reports on the role of KS to diagnose measles [10,12,18,19]; however, this is the first study to evaluate the test properties prospectively in current epidemiological conditions. The advantage of conducting such a study in London includes the unique combination of widespread community transmission of measles in a setting with good primary care services and high-quality laboratory testing. Nevertheless, the study results are applicable to other settings, particularly in developing countries, where primary care services may be less efficient and may not be supported by strong laboratory services.

Table 2. Preliminary and final logistic regression models for the prediction of confirmed measles.

Diagnostic odds ratios for correct measles diagnosis	dOR	lower CI	upper CI	Wald test p Value	LR test p Value
Preliminary model					
Koplik's spots present	8.61	2.15	34.49	0.002	0.012
Setting (hospital doctor vs. GP)*	3.96	1.02	15.34	0.047	0.043
Age > 5 years**	2.9	0.79	10.68	0.1	0.11
Reporting delay 2-3 days***	2	0.47	8.48	0.35	0.55
Reporting delay > 3 days***	0.77	0.12	5.19	0.79	
Final model					
Koplik's spots present	7.17	2.06	24.9	0.002	0.001
Setting (Hospital doctor vs. GP)*	4.32	1.29	14.5	0.018	0.016

The preliminary model is shown to demonstrate that reporting delays and age do not significantly contribute to explaining the variation in correctly diagnosing measles. Abbreviations: dOR = diagnostic Odds Ratios; CI = 95% confidence intervals; LR = Likelihood ratio. *Reference value is General Practitioner (GP); **Reference value is age < 5 years; *** Reference value is up to one day reporting delay.

We minimised reporting bias by prospective data collection and staff training; but residual reporting bias is possible. In particular, an unknown Koplik's status may have been misclassified as an absence of Koplik's and this is a limitation in our study. We believe that the potential for this bias is relatively small, because the observation of KS was made before laboratory confirmation was available (*i.e.*, independent of this).

In addition, we compared patients where the presence or absence of KS was recorded with those with missing KS information. The findings of similar measles positivity rates as well as a similar age, sex and reporter distribution in both groups suggest that exposure and ascertainment errors were not common and unlikely the source of significant bias.

This is a study using prospectively collected observational data to estimate test properties of Koplik's spots. Short of conducting a trial, underreporting of suspected cases remains a possibility, even in settings such as in the UK, where clinicians are required by law to report their suspicion to relevant health authorities, minimising the potential of underreporting. Milder cases are more likely to be underreported than severe ones; however, the occurrence of Koplik's spots has not been associated with disease severity and suspicion underreporting is unlikely to have introduced significant bias.

Well-established and highly sensitive and specific laboratory tests were used to confirm diagnosis. Samples were usually collected between one and six weeks after initiation of symptoms, optimising laboratory outputs. Equivocal samples or those taken too early to be confident about seroconversion were tested by PCR (to avoid testing false-negative). Testing of saliva samples has been well validated [5] and forms part of the UK routine surveillance system for measles.

In conclusion, we confirmed that clinical suspicion of measles has a low predictive value overall, but demonstrated that KS, while not "pathognomonic" as initially described by Henry Koplik [9], can significantly improve the accuracy of clinical diagnosis and help minimise false positive diagnosis. The lower predictive values in primary care emphasise the importance of clinicians keeping in mind their context and their local epidemiological variations. We have presented observational evidence on a relatively small sample and further studies should evaluate the added predictive value of including KS in clinical case definitions to improve early diagnosis and intervention.

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References

1. World Health Organization (date of publication) Immunization surveillance, assessment and monitoring.

Measles. Available: http://www.who.int/immunization_monitoring/diseases/measles/en/index.html. Accessed 25 November 2010.
2. WHO/ UNICEF (date of publication) Joint Statement. Global plan for reducing measles mortality 2006-2010.Available: http://whqlibdoc.who.int/hq/2005/WHO_IVB_05_11_eng.pdf. Accessed 25 November 2010.
3. Ramsay ME, Yarwood J, Lewis D, Campbell H, White JM (2002) Parental confidence in measles, mumps and rubella vaccine: evidence from vaccine coverage and attitudinal surveys. Br J Gen Pract 52: 912-916.
4. Health Protection Agency (date of publication) Confirmed cases of measles, mumps and rubella 1996-2008. Available: http://www.hpa.org.uk. Accessed 25 November 2010.
5. Brown DW, Ramsay ME, Richards AF, Miller E (1994) Salivary diagnosis of measles: a study of notified cases in the United Kingdom, 1991-3. BMJ 308: 1015-1017.
6. Vyse AJ, Cohen BJ, Ramsay ME (2001) A comparison of oral fluid collection devices for use in the surveillance of virus diseases in children. Public Health 115: 201-207.
7. World Health Organisation (date of publication) WHO-recommended surveillance standard of measles. Available: http://www.who.int/immunization_monitoring/diseases/measles_surveillance/en/index.html. Accessed 25 November 2010.
8. Ramsay M, Brugha R, Brown D (1997) Surveillance of measles in England and Wales: implications of a national salivatesting programme. Bull World Health Organ 75: 515-521.
9. Koplik H (1896) The diagnosis of the invasion of measles from a study of the exanthema as it appears on the buccal mucous membrane. Arch Pediatr 13: 918-922.
10. Steichen O, Dautheville S (2009) Koplik spots in early measles. CMAJ 180: 583.
11. Evans LM, Grossman ME, Gregory N (1992) Koplik spots and a purpuric eruption associated with parvovirus B19 infection. J Am Acad Dermatol 27: 466-467.
12. Annunziato D (1987) Koplik spots and echo 9 virus. N Y State J Med 87: 667.
13. Kirkwood BR and Sterne JAC (2003) Essential Medical Statistics. Oxford: Blackwell Science. 288 p.
14. Health Protection Agency (date of publication) Measles notifications (confirmed cases) England and Wales 1995 - 2009 by quarter. Available: http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1195733811358. Accessed 25 November 2010.
15. Hutchins SS, Papania MJ, Amler R, Maes EF, Grabowsky M, Bromberg K, Glasglow V, Speed T, Bellini WJ, Orenstein WA (2004) Evaluation of the measles clinical case definition. J Infect Dis 189: S153-S159.
16. Watson JC, Hadler SC, Dykewicz CA, Reef S, Phillips L (1998) Measles, mumps, and rubella--vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 47: 1-57.
17. Ramsay M, Manikkavasagan G, Brown K, Craig L (date of publication) Post Exposure Prophylaxis for Measles: Revised Guidance May 2009. Available: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1238565307587. Accessed 25 November 2010.
18. Aksit S, Caglayan S, Ozdogru E, Kansdy S (1994) Measles and absence of Koplik spots in vaccinated children. Paediatr Perinat Epidemiol 8: 455-456.
19. Porta IP, Bertone C, Baldassarre E (2008) Koplik spots in a measles-vaccinated child. Pediatr Infect Dis J 27: 853.

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